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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,908	05/27/2005	Minoru Asogawa	8074-1041	6557

466 7590 11/16/2007
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EXAMINER	
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ART UNIT	PAPER NUMBER
2881	

MAIL DATE	DELIVERY MODE
11/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/536,908	ASOGAWA ET AL.
	Examiner	**Art Unit**
	Bernard E. Souw	2881

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/13/2007 (Amendment).

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-7,10-12,16,21-26,30,31 and 34-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) 5-7,10,36 and 37 is/are allowed.

6)☐ Claim(s) 1-4,16,21-26,30,31,34,35,38 and 39 is/are rejected.

7)☒ Claim(s) 11 and 12 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 27 May 2005 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment and Argument

1. The Amendment and arguments filed 08/13/2007 have been entered. The present Office Action is made with all the suggested amendments being fully considered.

The abstract and the specification have been amended.

The claims have been amended.

New claims 36-39 have been added.

Claims 8 and 17 have been cancelled.

Claims 9, 13-15, 18-20, 27-29, 32 and 33 have been previously cancelled.

Claims 1-7, 10-12, 16, 21-26, 30, 31 and 34-39 are pending in this Office Action.

Objection to the Specification

2. The amended Abstract is objected to of the following informalities:

In lines 11-16:

"... a first external force ***[by which the external force is]*** imposed in the forward direction of the channel, and a second external force ***[by which the external force is]*** imposed in the direction opposite to the forward direction along the channel".

The two wordings, ***[by which the external force is]***, are not needed and should better be eliminated. Appropriate correction is required.

Applicant is obligated to also correct other errors of the same art that have not yet been hitherto identified due to limited space and time.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 21, 22 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carle et al. (USPAT 5,167,790) in view of Chan et al. (USPAT 6,696,022).

► As per claim 21, Carle et al. disclose a separation method using a separation apparatus shown in Fig.1, comprising

(a) a channel 16 through which a sample containing components-to-be-separated moves, as recited in Col.8/ll.34-37;

(b) a plurality of "compartments" provided to said channel ("compartment" broadly interpreted as lanes A,B,C,D,E defined by sample wells 17 in Fig.4, as recited in Col.11/ll.6-9); and

(c) an external force imposing unit 13,14 shown in Fig.1 and Fig.3, imposing external (electrophoretic) force to said components-to-be-separated (channel 16) so as to allow them to move through said channel, wherein said external force imposing unit has a function of alternately executing a first external force imposing pattern by which the external force is imposed to said components-to-be-separated in the forward direction along said channel, and a second external force imposing pattern by which the external force is imposed to said components-to-be-separated in the direction opposite to the forward direction along said channel (i.e., reverse-field electrophoresis), as recited in Col.3/ll.53-68 and Col.10/ll.66-68, to thereby fractionate said components-to-be-separated into any of said "compartments" (i.e., fractionated bands 1-8, contained in lanes A-E shown in Fig.4), as recited in Col.11/ll.6-39.

However, Carle's "compartment" is not truly a compartment, since it is not enclosed, as generally understood in the art under the term "compartment". Even farther away from true "compartment" are the bands 1-8. Chan et al. disclose a device shown in Fig.1 and Fig.2 for separating molecules based on their lengths (i.e., size), as recited in the Abstract/ll.4-6, Col.1/line 13, and Col.27/ll.28-39 & 51-66. Chan's "selection" has the same connotation as Carle's "separation", since in order to "select", Chan et al. must firstly separate or fractionate the sample, as Carle also does, as recited in Col.27/ll.34-39 + 51-67 and Col.28/ll.1-9. Chan's use of *electrophoresis* is

recited in Col.29/ll.15-20, more specifically in Col.31/ll.3-50, and especially in ll.19-25 and ll.30-35, thus rendering obvious the claim limitation that the external (electrophoretic) force allows the sample to move through the channel(s).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Carle's apparatus having open "compartments" with Chan's true partitions, or compartments or channels, since the enclosed compartment or channel structure allows a clean separation of the fractionated samples with little chance of inter-mixture, thus enhancing the resolution of the device.

One of ordinary skill in the art would have been motivated to use parallel channels that allow high resolution of separation, in order to achieve high throughput of sample separation (or selection, or screening, or in general sense, sample characterization), as taught by Chan et al. in Col.15/ll.61-64.

► Regarding claim 22, the migration ranges of the fractionated sample are shown by Carle et al. as bands 1-8 shown in Fig.4, as recited in Col.11/ll.6-39. Carle's migration range as shown in Fig.4 is caused by imposing the electrophoretic force, as recited in Col.10/ll.44-49 and Col.11/ll.6-15. Upon combining with Chan et al. using one of the embodiments shown in Fig.2(a)/3rd from top, 2(b), 2(d), 2(h) or 2(m)/bottom, Carle's migration range is to be matched to the length position of Chan's compartments, in order to fractionate the sample ***into*** Chan's compartments, thus rendering obvious the entire limitations of claim 22.

► As per claim 34, Carle's system comprises an external force switching control unit 13 shown in Fig.1 and 3, as recited in Col.9/ll.11-14.

5. Claims 16, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carle et al. in view of Chan et al., and further in view of Shimoide et al. (USPAT 7,105,354)).

Carle et al. as modified by Chan et al. show all the limitations of claim 16, as previously applied to the previously rejected independent claim 21, except the additional limitations of (a) a channel having a main channel and sub-channels formed as being branched out from said main channel; and (b) a main channel having one end where a sample introduction port is provided and the other end placed downstream of said one end (i.e., the sample introduction port).

Chan's embodiments shown in Fig.12, and more clearly in Fig.15, is provided with a sample introduction port, and the other end placed downstream of the sample introduction port, wherein the downstream (or flow) direction is unambiguously indicated by an arrow and also labeled as such. This embodiment is to be combined with Chan's other embodiments which are furnished with a main (central) channel and sub- (or side) channels formed as being branched out from said main channel, as shown in Fig.1(vii), 1(viii), (ix), (x), (xi), as recited in Col.20/ll.7-17, and Fig.2(c)/middle, 2(f), 2(j), 2(m)/top, as recited in Col.8/ll.28-30 + 65-67.

However, Chan et al. do not expressly recite in which direction the sample is moving, i.e., whether from the branches merging into the main channel, or from the main channel diverting into the sub-channels. Shimoide et al. expressly recite a particular embodiment in which the sample is diverted from the main channel into the

sub-channels, as recited in Col.26/ll.38-40 (as opposed to Shimoide's other embodiment recited in Col.11/ll.630-65 and Col.12/ll.55-670).

It would have been obvious to one skilled in the art that the purpose of the sub-channels is to fractionate the sample into the sub-channels, as taught by Shimoide et al., and to detect, extract or collect the fractionated components with higher resolution, as taught by Chan et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Carle's apparatus by Chan's plurality of sub-channels formed as being branched out from a main channel, since such a branching structure allows sample injection from a single inlet port, and yet multiple extractions of components from a plurality of collection ports, as taught by Shimoide et al.

One of ordinary skill in the art would have been motivated to use Chan's branching structure for achieving high throughput of the separation (or selection, or screening) process, as taught by Chan et al. in Col.15/ll.61-64.

However, neither Carle nor Chan et al. teach the last limitations of claim 16, i.e., "*............ so that a portion of said components-to-be-separated is moved to the downstream of the connecting position of said main channel and one of said sub channels in said main channel and subsequently imposing a second external imposing pattern having a different imposing direction ....*". This limitation is understood by those of ordinary skill in the art as imposing an external field in the downstream direction so as to move the components **pass a branching point** to a sub channel (moved to the downstream of the connecting position of said main channel and one of said sub channels), then followed by

(subsequently) imposing another field in the opposite direction, i.e., reverse electrophoresis.

This specific step is obvious to one of ordinary skill in the art, even without auxiliary teaching, but solely by following Carle's teaching of reverse field electrophoresis in combination with Chan's compartments as modified by Shimoide's sub channel. Upon repeating the periodic reversals of the electrophoretic field for a sufficient number of times, <u>such that some separated components would have passed beyond certain branching point(s)</u>, one of ordinary skill in the art would find some of the components already entered the sub channel, most probably when the field is reversed (of course, one of ordinary skill in the art --again without auxiliary teaching-- would apply a reverse voltage on the other end of the branch, since otherwise the reverse-field method would not be properly carried out). What remains to be done is merely a routine optimization to enhance the effect already observed.

► Claim 30 is a method claim reciting the same limitations as claim 16. Therefore, claim 30 is also rejected along with claim 16 over the same prior art references, including the pertinent reasons and motivations to combine.

► Regarding claim 31, the duration of Carle's external force in the first step (of claim 30), i.e., in the forward direction, is kept constant at 3 sec (while being repeated for 12 hours long), as recited in Col.10/ll.66-68.

6. Claims 1-4, 23-26 and new claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carle et al. in view of Chan et al., Anderson et al. (USPGPub 2001/00366720) and Pethig et al. (WO-97/34689).

► Carle et al. as modified by Chan et al. show all the limitations of claim 1, as previously applied to the other, previously rejected, independent claims 16 and 21, except the recitation of

(a) alternately executing a first external force imposing pattern by which the external force is imposed to said components-to-be-separated in the forward direction along said channel, and a second external force imposing pattern by which the external force is imposed to said components-to-be-separated in the direction opposite to the forward direction along said channel; and

(b) one, or two or more check valves disposed in said channel, partitioning the plurality of compartments and suppressing back flow of said components-to-be-separated.

Limitation (a) IS MADE OBVIOUS BY Carle et al. in col.3/ll.61-66 (reverse-field electrophoresis), further modified by Chan's capillary channels, as previously applied to the independent claims 16 and 21.

Limitation (b) is rendered obvious by Anderson et al. (USPGPub 2001/0036672) in view of Pethig et al. (WO-97/34689).

Anderson et al. disclose a fluid treatment device shown in Fig.3 that also includes sample separation channel (sect.[0011]/ll.3-5), in which electrophoresis is used to separate/analyze the sample, as recited in sect.[0083]/ll.1-6 and [0084]/ll.1-11,

particularly using the embodiment shown in Fig.3, which includes true compartments 202, 206, 210, 214 and 218, connected to fluid channels 208, 212 and 216, respectively, as recited in sect.[0111]/ll.1-6. Particularly regarding claim 1, a <u>check valve</u> is used in Anderson's separation apparatus, as recited in sect.[0112]/line 9, more particularly in sect.[0133]/ll.1-6 from bottom, and further, in sect.[0166]/ll.1-10. Anderson's check valve, as recited in sect.[0033], is functionally the same as Chan's obstacles, or posts, and hence, can be used to modify the latter.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Carle's apparatus having open "compartments" with Chan's true compartments that are further furnished with Anderson's check valves, since the check valve remains effective for the fractionated components as the only part that still moves within the channels, thus preventing the latter from leaking-back and mixing-up with the other fractionated sample(s) in the adjacent compartment(s).

One of ordinary skill in the art would have been motivated to modify Carle's & Chan's apparatus with Anderson's compartments separated by check valves as modified by Pethig et al., since the check valves allows a clean separation of the fractionated samples with little chance of intermixture, thus enhancing the resolution of the device.

► Regarding claim 2, Carle's channel extends in a straight form, as can be seen in Fig.1-4. Anderson's channels shown in Fig.3, 6A, and 6B are also straight in form. Thus, Carle's channel as modified by Anderson is also straight in form.

► Regarding claim 3, Anderson's check valve blocks a back flow of the fluid medium to an upstream side while moving it towards the downstream side of the channel, as expressly recited in sect.[0133]/ll.1-8 from bottom. Carle's reverse field technique as modified by Chan et al. imposes the external force (field) periodically, i.e., repeatedly, as recited in Applicant's claim 3. The rest of the limitations of claim 3 are the same as those of claim 21, which have been previously rejected as being obvious over Carle et al. as modified by Chan et al. Therefore, claim 3 is also rejected over the same prior art, but now with Anderson et al. and Pethig et al. just because of its dependency on claim 1.

► Regarding claim 4, the claim limitations is rendered obvious by Carle et al. in Col.3/ll.53-68.

► Regarding claim 23, the repeated steps of applying the external force within one compartment towards downstream, and then reversed towards the upstream, is rendered obvious by Carle et al., as recited in Col.3/ll.53-68.

► Regarding claims 24 and 25, the limitation that the duration of imposing external force is kept constant in every execution step of claim 23, i.e., in the forward as well as in the backward direction, is implicated by Carle et al. in Col.3/ll.65-66, wherein the external force in the forward direction is higher than the voltage applied in the reverse direction, in order to have a forward net migration of the samples, especially for molecules having very low differential mobility due to their very short conformation time relative to the reverse field interval or period, as taught by Carle et al. in col.5/ll.1-20 and col.6/ll.1-25.

► Regarding claim 26, the limitation that the duration of external force in the second step of claim 23 (upstream, in reverse direction) can be equal to, or longer than, in the first step (downstream, in forward direction) is inclusively implicated by Carle et al. in Col.3/ll.64-68, whereby it is self-obvious to simultaneously adjust the external force in the second step to be smaller than in the first step, in order to ensure a forward net migration of the sample.

► As per new claims 38 and 39, the two claim limitations are nothing else but a detailed description, how a flow blockage by Anderson's check valves works, so as to cause spatial separation of the components, wherein the recited "*suppressing portion*" is nothing else but the check valves, and the "*second external imposing pattern having a different imposing direction*" is nothing else but Carle's reverse electrophoresis field.

7. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carle et al. in view of Chan et al., Anderson et al. and Pethig et al., and further in view of Hancock et al. (USPAT 5,716,825).

Carle et al. as modified by Chan et al., Anderson et al. and Pethig et al. show all the limitations of claim 35, as previously applied to the parent claim 1, except the recitation of a specific mass spectrometric system being coupled to the sample separation apparatus of claim 1.

Hancock et al. disclose a MALDI/TOF mass spectrometry (MS) system, as recited in Col.11/ll.9-16, the MS system comprising:

A pre-treatment (or pre-analysis) unit separating a biological sample depending on the molecular size or properties, as recited in Col.11/ll.9-16 (wherein a DNA obviously represents a biological sample, as recited in Col.1/ll.46-55), and subjecting said sample to a pre-treatment (preparation) for an enzyme digestion treatment, the sample preparation or pre-treatment expressly recited in Col.7/ll.66-67 and Col.8/ll.1-10, whereas the enzyme digestion treatment is expressly recited in Col.2/ll.9-14; a unit subjecting said sample pre-treated by said pre-treatment unit to the enzyme digestion treatment, as already recited in Col.2/ll.23-24; a drying unit drying the enzyme-digestion-treated sample, as recited in Col.10/ll.39-46; and a mass spectrometry unit subjecting the dried sample to mass spectrometry, as recited in Col.10/ll.59-63, wherein the term "*dried*" being expressly recited in line 61. The limitation that Hancock's microchannel system including the pre-treatment unit comprises a miniaturized unit, is recited in Col.3/ll.1-20, more specifically as "*microchannel*" and "*chip*" in Col.4/ll.34-55.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to couple Hancock's mass spectrometer system to the sample separation apparatus of Carle et al. as modified by Chan et al., Anderson et al. and Pethig et al., in order to determine and/or identify not only the size, but also the mass and the molecular constituents of the fractionated sample.

One of ordinary skill in the art would have been motivated to modify the sample separation apparatus of Carle et al., Chan et al., Anderson et al. and Pethig et al., particularly with Hancock's MALDI/TOF spectrometer, since the latter not only is capable of fragmentizing the fractionated sample, but is further equipped with a number

of processes relating to enzyme digestion treatment and/or research, all those in the form of a tiny microchip that would allow automated and batch processing.

Final Rejection

8. In spite of Applicant's amendment, **NO** new ground of rejection is presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP §706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ALLOWANCE

9. Claims 5-7, 10, 36 and 37 are allowed

Reasons for Allowance

10. The following is a statement of reasons for allowance:

► Independent claim 5 (amended) is allowed for reciting the limitation of "*imposing patterns having different imposing directions from each other to said components-to-be-separated so as to allow them to move through a channel*", wherein the first imposing pattern has a certain direction so that a portion of said components-to-be-separated is intercepted by one of the bent portions of the channel, and <u>the subsequent (second) pattern has a direction different from the previous direction such that the portion of the components-to-be-separated that has been previously intercepted by said one of said bent portions is now moved to the downstream next compartment</u>.

► Claims 6, 7, 10, 36 and 37 are also allowed for their dependency, either directly or independently, on the previously allowed claim 5.

Indication of Allowable Subject Matter

11. Claims 11 and 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Reasons for Indication of Allowable Subject Matter

12. The following is a statement of reasons for the indication of allowable subject matter:

► Claim 11 is allowable for reciting the limitation that the length of a channel placed on the further downstream side has a larger length, which may result in equal migration times required by the fractionated components to move forward within each successive

compartment. Whatever purpose Applicant has in mind, it is non-obvious to require larger lengths for channels placed further downstream. This is a unique design choice having a special purpose that underlines Applicant's invention not anticipated or rendered obvious by any prior art.

► Claim 12 is allowable for reciting the limitation that a smaller external force is to be applied to a channel placed further downstream, which also may result in about the same migration time required by the fractionated components to move forward within each successive compartments (since the fractionated component further downstream moves forward at a higher migration velocity). Again, irrespective of whatever purpose Applicant has in mind, it is non-obvious to require a smaller external force to be applied to a channel placed further downstream. This is another unique design choice underlining Applicant's invention not anticipated or rendered obvious by any prior art.

Response to Applicant's Arguments

13. Applicant's argument on pg.30 that "*Chan does not disclose compartments*" is simply not true. Applicant's entire disclosure does not provide distinction between "*compartments*" and "*partitions*". Even if the partitions are separated by check valve, Applicant's compartments are nothing else but partitions separated by regions having enhanced flow resistance, as recited in PGPub 2006/0063273 sect. [0013], or in the disclosure pg.4/ll.18-27 and pg.5/ll.1-23:

> Disclosure [0013]: The check valves per se herein are preferably composed of a material not electrically affective to the components-to-be-separated in the sample. The check valves <u>may</u> typically be configured by a plurality of <u>columnar structures</u> arranged at intervals narrow enough to prevent the components-to-be-separated from passing therethrough. Materials for composing the check valve may be anything provided that they are not electrically affective to the components-to-be-separated in the

> sample as described in the above, and may typically be a conductive member. The check valves herein are successful enough if they can function as valves, and may be formed so as to have a variety of structures and geometries.

In this regard, Applicant's columnar structures are similar to Chan's posts, or Anderson's valves as recited in sect. [0033]:

> Anderson [0033]: FIG. 12A-C show a schematic representation of a miniature integrated device employing a pneumatic fluid direction system utilizing a gas permeable fluid barrier bound vents, e.g., a poorly wetting or hydrophobic membrane,and pneumatically controlled valves. FIG. 12A shows an embodiment of a single chamber employing this system. FIG. 12B is a schematic illustration of a debubbling chamber for linking discrete fluid plugs that are separeted by a gas bubble. FIG. 12C schematically illustrates this system in an integrated device having numerous chambers, including degassing chamber, dosing or volumetric chamber, storage and reaction chambers.

Thus, Applicant's "*compartments*" do not distinguish from Chan's partitioned channels illustrated in Figs. 2(a), 2(b), ... etc. , with or without valves or fluid plugs, i.e., Chan's obstacles, posts or narrow/bent channels, as illustrated in Fig.2(a) (3rd row from top), Fig.2(b) and Fig.2(m). Their primary function is the same, i.e., to prevent components-to-be-separated from passing, so as to enhance the separation and its resolution.

Therefore, Applicant's argument that Chan's and Anderson's compartments do not obviate Applicant's compartment is unpersuasive.

14. Applicant's check valve, as described in sect.[0013] of PGPub 2006/0036672, or in the disclosure pg.4/ll.18-27 and pg.5/ll.1-2, is similar to Anderson's valve, as described in sect.[0033], i.e., no other than fluid plugs having resistance to fluid flow and/or component migration across channel sections, or compartments. Such "valves" are thus similar to Chan's obstacles, posts or narrow (or bent) channels, as illustrated in Fig.2(a), 2(b) and etc. Both Applicant as well as Anderson et al. allow varieties beyond

embodiments described in the text. Therefore, Anderson's valve is here used to modify Chan's obstacles/posts/narrow or bent channels, just in order to carry the name "valve" as recited in Applicant's claim(s). The flow of fluid thereby involved may be quite small, as recited by Chan et al. in col.29/ll.7-15 & 42-43. The interchangeability between Chan's and Anderson's "valve" is further discussed in the Examiner's Response to Applicant's Arguments at the end of this office action.

Anderson's method (based on reaction chambers) is carried out by applying differential pressures to the compartments (reaction chambers) to transport the fluid, as recited in sect.[0010], [0015] and [0016]. However, depending on the flow resistance, this pressure difference may be quite small and unappreciable, as recited by Chan et al. in col.29/ll.7-15 & 42-43. Anderson's reaction chambers may be replaced with fluid separation channels, as taught by Anderson et al. in sect.[0011]/ll.1-5, in which sample transport is accomplished by electrophoretic method, as recited in sect.[0083]/ll.1-6 and [0084]/ll.1-11. In this regard, Pethig et al. teach that in a sample separation technique using electrophoretic force, in which the fluid medium itself does not need to flow through the channel(s), as recited in the Abstract/ll.2-5. Therefore, in Carle's apparatus as modified by Anderson's check valve, it is the component-to-be-separated which are blocked from back-flow by the check valve, since the fluid itself is hardly in motion.

Anderson's fluid flow technique can be combined with, or substituted with Chan's high/low flow rate technique to move the molecules forward and separate them into compartments. As already applied to the previous rejection of claim 21, Chan's reverse flow technique recited in col.29/ll.15-20 is the same or equivalent to Carle's reverse or

high/low voltage electrophoretic technique recited in col.6/ll.1-25, all resulting in separation or fractionation of the components according to their differential mobilities.

Therefore, Applicant's argument that Anderson's valve can not be used in Applicant's case, or substitute Chan's obstacles/posts/narrow or bent channels, on the ground that such valve works by pressure difference, is not based on proper physics. Depending on the pertinent flow resistance, the required pressure difference and the resulting fluid flow may be quite small and negligible, especially if narrow or bent channel is used as valve, as taught by Chan et al. in col.29/ll.7-15 & 42-43. Pressure difference always exists, even using Carle's transport medium with pores to provide fluid resistance that separates or fractionates the components. Therefore, Applicant's argument that Anderson's valves can not be used in Applicant's case, or to substitute Chan's obstacles/posts/narrow or bent channels, on the ground that it works by pressure difference, is unpersuasive, simply because Applicant's compartments and valves also require pressure difference. Note also, Anderson's valve is here used to modify Chan's obstacles/posts/narrow or bent channels, just in order to carry the name "valve" as recited in Applicant's claim(s). In fact, their structure, purpose and function are the same.

15. Applicant's argument regarding incompatibility of the references used is based on a misunderstanding of the main references, i.e., Carle et al. and Chan et al., as well as the examiner's rejections:

Carle's mechanism of electrophoretic transport as described in col.5/ll.1-20 is exactly the same as Chan's electrophoretic transport described in col.29/ll.15-20. In particular, Carle's DNA molecules are stretched like spaghetti with regard to directional conformation of the long molecule strain in the electrophoretic field (Carle col.6/1-25). If the reverse field interval or period matches (or less than) the molecule's conformation time, the electrophoretic mobility is very low (Carle col.5/ll.1-20). Carle's molecular conformation time also applies to Chan's DNA molecules, i.e., the time for the molecule to stretch (uncoiled) and become elongated like spaghetti under a forward field, as recited in col.29/ll.15-20, especially lines 18-20. Reverse field electrophoresis like Carle's is also used by Chan, as recited in col.29/ll.15-20, specifically implicated in line 20. Thereby, one of ordinary skill in the art also understands that Carle's reverse field is the same or equivalent to Chan's reverse flow, whereas Chan's high/low flow rate is equivalent to Carle's high/low electrophoretic voltage, both resulting in separation or fractionation of the components according to their differential mobilities. Chan's molecules that do not stretch fast enough in a forward field are moving only slowly forward, thus lagging behind those which uncoiled and stretch rapidly enough to conform with the forward field. If the field is reversed (or decreased) the molecules may recoil, but that is irrelevant. The molecules will uncoil again and move forward when the forward field is restored. Carle's method and Chan's method remain in **excellent agreement** even using Chan's **posts** for dividing the compartments (shaded part in Chan's Fig.2(b)), since the stretched, spaghetti-like, molecules can pass easily through Carle's pores recited in col.6/ll.14-16, or Chan's posts dividing the compartments. On

the other hand, those which do not unravel or stretch fast enough do not pass the obstacles and become separated from those which have passed.

In particular, Chan's embodiment shown in Fig.1 (xxi), recited in Col.20/ll.42-43, seems appropriate to one skilled in the art for enclosing Carle's lanes A-E within parallel channels or compartments, i.e., each of Chan's five channels enclosing each of Carle's five lanes. As a result, each lane or channel of Fig.1(xxi) contains one or more fractionated samples (=bands), i.e., bands 1-2 in channel A, band 3 in channel B, band 4 in channel C, band 5 in channel D and bands 6-8 in channel E. The claim limitation "*to thereby fractionate said components-to-be-separated into any of said compartments*" is more precisely satisfied by giving each channel of Fig.1(xxi) the form of a series of <u>compartments</u>, or <u>partitions</u>, as shown in Fig.2b and Fig.2m, either with or without dividing posts, wherein the length of each compartment is made to match the migration distance of the fractionated species and the applied electrophoretic force (with or without obstacles or posts). This match depends on Carle's molecular conformation time and is further determined by Chan's molecular stretch

Such modification is enabled because applicant's disclosure does not provide distinction between "*compartments*" and "*partitions*". See also previous explanation regarding the interdependence of migration distance/velocity (as determined by Carle's molecule's conformation time) with Chan's molecular stretch.

16.

Regarding the examiner's rejection, Applicant has repeatedly cited passages from the two references that have never been cited or used by the examiner in the

rejection. The teaching of Carle et al. that was used in the examiner's rejection is the reverse-field electrophoresis. Of course the Carle's reference does not teach compartments; otherwise it would have been a §102 rejection. The Chan's reference was cited with regard to the use of compartments to remedy the deficiency in Carle's. Of course, Chan et al. does not disclose moving the sample in the reverse direction, as alleged by Applicant on pg.29 of his arguments; this teaching is provided by Carle et al.

However, Applicant has made a grave mistake with his argument on pg. 28:

> As the object of CHAN is to stretch the molecules, if the reverse direction of the external force is imposed, the <u>stretched molecules become original circle structure</u> and thus <u>the object of CHAN cannot be obtained</u>.

Who cares about "*the object of CHAN*"? Similarly, who cares about Chan's "*tapered structure*", as recited by Applicant on pg.28? The examiner's rejection does not need any of those recited by Applicant. It is Applicant alone, not the examiner, who held Chan's tapered structure essential. However, just because Chan's stretched molecules "*become original circle structure*", Chan's molecules behaves exactly like what is needed for Carle's reverse field electrophoresis, i.e., to cause different mobilities according to the molecules' ability to stretch in a forward field. This mobility depends on the time and the extent the molecule is stretched and becomes like "spaghetti", as described by Carle et al. in col.5/ll.5-20:

> Under steady-state electrophoresis, a molecule can be regarded schematically as an arrow, in which the leading portion of the molecule is in a different <u>conformation</u> than the trailing portion. The model assumes that a molecule has a much higher mobility when the arrow is aligned with the field than when it is oppositely aligned, or perhaps even in some intermediate <u>conformation</u>. It is also assumed that a size-dependent time interval is required for a molecule to invert the directionality of its <u>conformation</u>. When the field-inversion cycle has a period that is closely matched to the interval required for a particular sized molecule's conformational inversion, that molecule has very low mobility since it spends little or no time in a <u>conformation</u> that is appropriately aligned with the field.

And further, in col.6/ll.10-25:

> The ability of a modulated field to effect separations in a manner similar to that obtained by field-inversion also relies on differential changes in conformation. For long, narrow molecules such as DNA chains or denatured proteins, the migrating materials may behave more or less like "spaghetti". If a relatively low voltage is imposed across the support, the spaghetti has time to unravel itself and migrate cleanly through the pores in the direction corresponding to the electric field interacting with its charge. On the other hand if the voltage is suddenly spiked the charged portions across the entire length of the molecule are suddenly thrust against the barriers in the matrix preventing successful forward motion. Thus, when extremely steep and high magnitude voltage fields are applied in the "forward" direction, alternating with low voltages, migration rate also depends on the rate of reconformation and, in field modulation, the "reverse" direction can, in a sense, be mimicked by the forward voltage.

Thus, Carle's *conformation* that determines the molecules differential mobility depends on the ability of the DNA molecule to stretch like spaghetti, just as taught by Chan et al. and cited above by Applicant. Those molecules that can stretch rapidly within one period of the forward voltage have a high mobility. Those that are late with stretching have a lower mobility. Thereby it is totally irrelevant, whether or not the molecule would "*become original circle*" when the field is reversed, as alleged by Applicant.

Carle's forward motion due to molecular stretch under electrophoresis is also employed by Chan et al., as recited in col.4/ll.55-60:

> DNA has also been stretched by electrophoresis without fixing one end of the molecule. As part of a near-field detection scheme for sequencing biomolecules, DNA has been elongated by electrophoresis both in a gel and in solution, using electrical forces to move the DNA in position for reading.

Chan's forward motion under electrophoresis can also be accomplished by fluid flow, as in Anderson's, or by similarly modifying the field lines (e.g., by alternating between high and low voltages, as taught by Carle), as recited in by Chan et al. in col.29/ll.15-20:

> Polymers driven by fluid flow (induced by any of the later-cited methods such as pressure differential and gravity) will principally follow the fluid flow lines (in electrophoresis for charged biopolymers, the polymer follows the field lines, which can be similarly modified).

It is thus clear, Carle's electrophoresis technology, either the reverse-field or the varying/alternating field, is based on Chan's stretching and recoiling of DNA molecules. These techniques are also equivalent to the microchannel fluid separation technology

based on fluid flow using pressure differentials, as in Anderson's, in which check valves are used. All these separation techniques belong to the same analogous art, and hence, they can be interchanged, combined and/or substituted with each other, as applied by the examiner in this office action.

Therefore, the entire Applicant's argument is based on a wrong premise, i.e., wrong understanding of the cited references as well as the examiner's ground of rejections. As such, Applicant's arguments are unpersuasive and can be totally dismissed.

Communications

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bernard E Souw, Ph.D., whose telephone number is 571 272 2482. The examiner can normally be reached on Monday thru Friday, 9:00 am to 5:00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Kim can be reached on 571 272 2293. The central fax phone number for the organization where this application or proceeding is assigned is 571 273 8300 for regular communications as well as for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571 272 5993.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

B. Souw
October 17, 2007

ROBERT KIM
SUPERVISORY PATENT EXAMINER